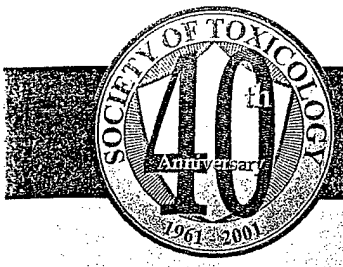

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skin surface may alter the disposition of permethrin in skin and possibly its bioavailability in soldiers simultaneously exposed to these chemicals if these results mimic human exposure. (Supported by USAMRMC Grant, DAMD-17-99C-9047).

613 STEREOSELECTIVE ABSORPTION OF PERMETHRIN THROUGH SILASTIC MEMBRANE AND EXCISED PORCINE SKIN *IN VITRO* FLOW THROUGH DIFFUSION SYSTEM.

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Permethrin has four isomers, two of which have insecticidal activity (1R-cis- and 1R-trans-). During the Gulf War, soldiers were exposed to certain insecticides that included permethrin as well as other chemicals. The purpose of this study was to determine if differential absorption occurs between trans-permethrin and cis-permethrin in the silastic membrane and the excised porcine skin in an *in vitro* flow through diffusion system. The silastic membrane and porcine skin was dosed with 14C-permethrin containing approximately 48+/-1% of the trans-permethrin isomer and 52+/-1% of the cis-permethrin isomer. Perfused samples were collected at various time points over an eight hour period. Representative samples from the 90 minute, 8 hour and peak absorption times were extracted and the isomers were separated by HPLC. Based on total radioactivity, preliminary results suggest that the trans-permethrin isomer is absorbed more readily than the cis-permethrin isomer in the silastic membrane. Work is currently underway to investigate absorption in the excised porcine skin. (Supported by USAMRMC Grant, DAMD-17-99C-9047).

614 DERMAL UPTAKE OF PESTICIDES DURING EXPOSURE EVENTS WITH INTERMITTENT SURFACE CONTACT: MALATHION CASE STUDY.

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The goal of this study is to select a dermal uptake model that simulates dermal adsorption and absorption of pesticides such as malathion on the hands following short-term contact, and is compatible with PBPK models. Existing dermal uptake models address uptake of chemicals from relatively long-term (near steady-state conditions) during contact with water, soil, and other carrier vehicles (*e.g.*, creams, cloths). These models are not appropriate for assessing uptake from short-term (seconds to minutes) and intermittent contacts with chemical residues on surfaces treated with liquid, powder and granular pesticide. To address this issue, we developed a model to predict diffusive fluxes of compounds through the epidermis using a finite-difference discretization applied to Fick's second law. The model can estimate the skin uptake as a function of time and depth and is calibrated with studies on the rate of malathion penetration in rats. Tape stripping data were collected after 1, 4, and 12 hours of exposure. Both the newly developed discretized model and equivalent one-compartment models are evaluated for predicting the observed exposure and uptake. The fully discretized model was used to develop an equivalent, but simpler compartment model that can be linked with PBPK models. This model estimates total uptake to blood from transient contacts using steady-state permeability (K_p), skin loading, a partition factor and contact time. Although total uptake can be a nonlinear function of contact duration, we have discovered a range of contact times and contact regimens for which uptake to blood is not sensitive to boundary assumptions and is a simple linear function of cumulative contact. We are developing both in vivo and *in vitro* protocols to continue model evaluation. This work has been funded wholly or in part by the United States Environmental Protection Agency. It has been subjected to Agency review and approved for publication.

615 EXPOSURE TO SULFUR MUSTARD CAUSES A CONCENTRATION DEPENDENT LOSS OF INHIBITORY ACTIVITY OF ALPHA$_1$ ANTITRYPSIN.

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Sulfur mustard (SM) is a potent vesicating agent that causes, in human skin, a separation at the dermal-epidermal junction leading to the formation of large fluid filled blisters. The mechanisms of blister formation have not been elucidated, but there appears to be proteolytic cleavage at the sites of SM exposure resulting in large fluid filled bullae. Possible mechanisms for the proteolytic cleavage at these sites of SM exposure are the decrease in protease inhibitor capacity and/or the increase in protease activity. To determine whether SM exposure could initiate loss of protease inhibitor activity, alpha$_1$ antitrypsin (α_1-AT), the major antiprotease at the dermal-epidermal junction, was exposed to various concentrations of SM and its resulting inhibitory capacity was determined. The effect of SM on α_1-AT inhibitory capacity was measured by incubating α_1-AT with various concentrations (10^{-4} to $2x10^{-3}$ M) of either SM or hydrolyzed SM for 1 hr at 37° C. The resulting α_1-AT solutions were mixed with trypsin for 30 mins at 37° C before being added to a 96-well plate containing benzoyl-DL-arginine-p-nitroanilide (BAPNA), a trypsin substrate, and the optical density of the wells was determined at 405 nm. The loss of the ability of SM-treated α_1-AT to inhibit trypsin was determined by the increase in optical density from the cleavage of benzoyl-DL-arginine-p-nitroanilide by the still active trypsin. Loss of α_1-AT activity was detected at concentrations as low as $3x10^{-4}$M SM and reached its maximum of a 30% decrease at $1.5x10^{-3}$M SM. The hydrolyzed SM did not demonstrate any ability to decrease the inhibitory activity of α_1-AT. It appears that SM can cause a decrease in the inhibitory activity of α_1-AT, but it has not yet been determined whether this SM initiated decrease in inhibitory capacity is significant enough to result in increased proteolytic activity at the dermal-epidermal junction and the formation of blisters.

616 TOXICOKINETICS OF TOPICALLY APPLIED SULFUR MUSTARD IN THE FUR-COVERED AND HAIRLESS GUINEA PIG SKIN: EFFECT OF IODINE AND HYPOCHLORITE.

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Sulfur mustard (SM) is a powerful vesicant used as chemical warfare. In the present study skin levels of SM were quantitatively measured in the fur-covered and hairless guinea pig models. Wells were constructed on the back of an anesthetized animal by the following procedure. A plastic tube was cut to form open-ended cylindrical wells and a thin layer of commercial silicon sealing ointment was applied to one edge of the wells. The wells were then attached to the animals back so that liquid inside the wells did not leak out. The center of each well was exposed to 1.2mg SM (neat liquid). At certain time intervals after exposure methylene chloride (0.5 ml) was applied into each well for extraction of SM from the skin of the living animal. SM was quantified by gas chromatography/mass spectrometry analysis. Measurements taken 30 and 60 min after exposure of male guinea pig showed SM reduction by 44% and 99.4%, respectively. In the female the rate of SM disappearance was slower, namely, decrease of 39%, 82% and 99.6% was observed 60, 120 and 180 min after exposure, respectively. Iodine and sodium hypochlorite did not significantly alter skin SM levels in comparison to the effect of their vehicles. The male hairless guinea pigs showed similar pattern to that observed in the haired guinea pigs. Low levels of skin SM were detected after termination of exposure to SM vapor in both animal models. These findings indicate that the rate of penetration of neat liquid SM and its reaction with skin components is within tens of minutes and even hours after exposure. The fact that iodine does not affect the vesicant is important for understanding the mechanism of iodine-induced protection against SM. (supported by the U.S. Army Medical Research and Material Command under Cooperative Agreement No. DAMD17-98-2-8009).

617 GENE ARRAY ANALYSES OF SULFUR MUSTARD-INDUCED INFLAMMATORY MEDIATOR RESPONSE IN MOUSE EARS.

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As part of the Medical Chemical and Biological Defense Research Program, the U.S. Army Medical Research Institute of Chemical Defense has a mission to identify biomarkers predictive of exposure to vesicating agents such as sulfur mustard [bis(2-chloroethyl) sulfide; HD]. Previous reports from this laboratory established that HD influences inflammatory gene expression in several *in vivo* models of vesicant injury. Gene expression arrays were used to profile HD-induced gene expression in ear tissue of CD1 mice. Adult, male mice were treated topically with HD (0.16 mg) on the medial surface of the ear. At 3, 6, 12, or 24 hr following exposure, biopsies were collected. RNA was isolated and complementary deoxyribonucleic (cDNA) probes were radioactively labeled using gene-specific primers. Labeled cDNA probes were hybridized to 588-gene expression arrays and phosphorimager